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Patentanmeldung Nr. Patent application No. Demande de brevet n°

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Der Präsident des Europäischen Patentamts;
Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets
p.o.

R C van Dijk

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Anmelder/Applicant(s)/Demandeur(s):

Boehringer Ingelheim International GmbH
Binger Strasse 173
55216 Ingelheim am Rhein
ALLEMAGNE

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(Falls die Bezeichnung der Erfindung nicht angegeben ist, siehe Beschreibung.
If no title is shown please refer to the description.
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Combinations of Epinastine, Pseudoephedrine and Methylephedrine as new pharmaceutical formulations

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years, desensitisation therapy, which decreases the sensitivity of living body against allergen, has been tried, but people don't completely recover, and the problem that the therapy needs long term for treatment is not resolved. Consequently, the drug administration to remove or decrease the various symptoms has been prevailing for now.

It is desirable for a drug for common cold or allergic disease treatment to remove or decrease these various symptoms, but such a remedy has ever been unknown.

For example, H1 antihistaminics are effective to relieve the symptoms such as snooze and itch, but it is no necessarily effective to remove or decrease the symptoms such as nasal congestion (blocked nose), rhinorrhea (nasal discharge), eye itch, and cough.

A medical composition with inhibitory effect on overactive airway secretory gland function such as rhinorrhea (nasal discharge) comprising an anticholinergic drug and a H1 antihistaminic drug is disclosed by JPA10298107.

Another medical composition with effect on nasal congestion (blocked nose) comprises loxoprofen and a H1 antihistaminic drug and is disclosed by JPA2001-199882.

WO98/06394 discloses a composition of H1 antihistaminic drug and a H3 antihistaminic drug.

WO99/32125 discloses such a composition of a leukotriene antagonist and antihistaminic drug.

These compositions try to treat the symptoms which stem from common cold or allergic diseases, although the symptoms are not yet treated optimally. In particular, this is true for symptoms which stem from common cold, rhinitis or allergic diseases like nasal congestion and frequently coughing.

Combinations of Epinastine, Pseudoephedrine and Methylephedrine as new pharmaceutical formulations

The present invention relates to novel oral pharmaceutical compositions comprising as pharmaceutically active compounds a combination of an antihistaminic-effective amount of Epinastine or a pharmaceutically acceptable salt thereof and decongestant-effective amount of Pseudoephedrine or a pharmaceutically acceptable salt thereof plus Methylephedrine (Methylephrine) or a pharmaceutically acceptable salt thereof. The formulation further comprises suitable pharmaceutically acceptable carriers or excipients. Another aspect of the present invention relates to methods for the preparation of these compositions and methods of using them in the treatment of symptoms which stem from common cold, rhinitis, rhinorrhea (nasal discharge) and nasal congestion (blocked nose), cough, sputum, allergic diseases and/or disorders like saisonal allergic rhinitis (SAR) and saisonal allergic conjunctivitis (SAC).

Background of the invention

Common cold is a disease which develops various symptoms caused by contagious virus infection of nasal cavity, paranasal cavity, pharynx or airway. The variety of symptoms such as rhinorrhea (nasal discharge), nasal congestion (blocked nose), sneeze, soar throat, cough, muscle pain, headache are shown, and the types of virus causing such symptoms are said to be more than 200.
There was no direct treatment, and the only treatment is drug administration to remove or decrease the various symptoms.

On the other hand, allergy is a general term of symptoms accompanied by immuno-reaction, various substance such as food, drugs, pollen, house dust, auto emission are quoted as causative agents (allergen). Especially in recent years, seasonal allergy whose main allergen is pollen and perennial allergy whose allergen was itch and house dust have increased. Symptoms which stem from these allergies are such as nose/pharynx itch, snooze, rhinorrhea, nasal congestion, cough, asthma, eye itch, eye congestion, foreign body feeling of eye, and various as well as symptoms which stem from common cold. Removing the allergen is the best way as treatment, however, it is often difficult to remove the allergen compl t ly in daily life. In recent

Epinastine, 3-amino-9, 13b-dihydro-1H-dibenz (c, f) imidazo (5, 1-a) azepine, is an H1 antihistaminic active compound. For medical purpose, it is usually used as hydrochloride salt, but the present invention is also related to other pharmacologically permissive acid-additions salts or the free base.

Epinastine did not yet show strong treatment effects on rhinorrhea, nasal congestion, and cough.

Methylephedrine is one of many alkaloids contained in *ephedra* and has sympathetic nerve stimulant action.
The term Methylephedrine comprises the dl form and l form, and any of them can be used for the present invention. Besides, if pharmacologically permissive salts such as Methylephedrine hydrochloride is used, the effect is not different.

Pseudoephedrine used for the present invention is also contained in *ephedra* and also has sympathetic nerve stimulant action. The term Pseudoephedrine comprises the d form, l form, and dl form and the stereoisomer, and any of them can be used for the present invention. Besides, if pharmacologically permissive salts such as Pseudoephedrine hydrochloride and Pseudoephedrine sulfate are used, the effect is not different.

Surprisingly, it was found out that a composition composed of Epinastine, Methylephedrine and Pseudoephedrine is highly effective on decreasing rhinorrhea and nasal congestion, symptoms which stem from common cold or allergic diseases.

Furthermore, it was found out that the compositions composed of Epinastine, Methylephedrine and Pseudoephedrine, additionally was also effective in treating cough.

According to the invention the term pharmaceutically acceptable or permissive salts stands for acid addition salts of the active compounds Pseudoephedrine, Epinastine and/or Methylephedrine. These acid addition salts can be formed with inorganic acids like hydrochloric acid, hydrobromic acid or sulfuric acid or with organic acids as for instance oxalic acid, fumaric acid or methansulfonic acid. Epinastine is preferably

Therefore it is an objective of the present invention to develop a pharmaceutical composition which can remove or decrease these symptoms caused by common cold or allergic diseases.

Description of the present invention

It now was found that the combination of epinastine, an H1 antihistaminic agent with antitussive activity and the decongestants Pseudoephedrine and Methylephedrine successfully treat the symptoms of the above mentioned diseases.

It is one objective of the present invention to treat the symptoms of cough and cold diseases and allergic rhinits or conjunctivitis, i.e. sneezing, itching, blocked nose, runny nose cough and all together.

Another objective is to develop a suitable pharmaceutical formulation for treating congested Eustachian tubes and / or the ways of the respiratory system.

Another objective of the present invention is the treatment of common cold and in the symptomatic relief associated with cough, cold and flu symptoms.

Still another objective of the present invention is to overcome the disadvantages of the medications known in the art in the treatment of SAR and/or SAC.

Description of the invention

The present invention solves the aforementioned problems of the state of the art formulations of insufficient treatment of the aforementioned diseases by providing a pharmaceutical formulation comprising an antitussive-effective amount of Epinastine or a pharmaceutically acceptable salt thereof and of a decongestant-effective amount of Pseudoephedrine or a pharmaceutically acceptable salt thereof in combination with Methylephedrine or a pharmaceutically acceptable salt thereof. Further ingredients of the formulation of the present invention may be pharmaceutically acceptable carriers or excipi nts.

cholecalciferol, tocopherol acetate, and nicotinamide; antacids such as magnesium carbonate, aluminium sulfate, and magnesium aluminometasilicate; crude drugs such as puerariae radix, licorice, cassia, and bupleurum root.

In a preferred embodiment the present invention relates also to an oral pharmaceutical composition. It is preferred that the composition of the present invention is prepared for oral administration formulation. Such formulations can be manufactured by methods well known in the state of the art and comprise tablets, granules, fine granules, powders, capsules, chewable tablets, goumis, drops, foaming agents, resolvents in mouth, dry syrup and so on. Due to the short-lasting effects of Pseudoephedrine and Methylephedrine and - relatively to this – the long-lasting effect of Epinastine it might be of advantage to have a sustained release of Pseudoephedrine and/or Methylephrine and an immediate release of an antihistaminic effective amount of epinastine.

The preferred dosage forms are tablets or capsules.

The composition also may comprise additives. In case of solid formulation, the additives may be selected from the group of: excipients such as lactose, starch, sugar, mannitol, and microcrystalline cellulose; binding agents such as hydroxypropylcellulose, hydroxypropylmethylcellulose, gelatine, and PVP; disintegrating agents such as carboxymethylcellulose calcium and low substituted hydroxypropylcellulose; lubricants such as magnesium stearate, cured ricinus, and talc. Other than the above, solubilizing agents, buffers, preservatives, perfumes, pigments, corrigents and so on are can be used if necessary. Other additives that may be used are mentioned below.

Concerning the application via a tablet, in the context of the present the invention a bilayer tablet might be of advantage. In such a bilayer tablet there may be a first layer A which provides for the sustained release of Methylephedrine and Pseudoephedrine or a pharmaceutically acceptable salt thereof, which are comprised in a decongestant effective amount. A second layer B provides for the immediate release of Epinastine and comprises an antihistaminic effective amount of Epinastine or a pharmaceutically acceptable salt thereof.

used as its hydrochloric acid addition salt. Pseudoephedrine and also Methylephedrine are preferably used as the hydrochlorides or the sulfates. Within the present invention the hydrochloride-salts for the latter two compounds are most preferred.

In context of the present invention Epinastine or its pharmacologically permissive salts may be blended with the other active ingredients in an amount of 2 to 25 mg as daily dosage for adults, 4 to 20 mg is more preferable, and 5 to 10 mg is most preferable.

The amount of Methylephedrine or its pharmacologically permissive salts is 10 to 240 mg as daily dosage for adults, 25 to 150 mg is more preferable, and 50 to 110 mg is most preferable.

The amount of Pseudoephedrine or its pharmacologically permissive salts is 10 to 300 mg as daily dosage for adults, 25 to 250 mg is more preferable, and 100 to 240 mg is more preferable.

Also the above mentioned active ingredients are the preferred ones and as a consequence thereof the formulation preferably does not contain any further active ingredients, the formulation of the present invention is not limited to theses active ingredients alone. As an additional active compound the compositions according to the invention may optionally contain one or several compounds selected from the group consisting of antipyretic and analgesic drugs such as acetaminophen, aspirin, and ethenzamide; nonsteroidal anti-inflammatory agents such as indomethacin, diclofenac sodium, ibuprofen, ketoprofen, and piroxicam; antiallergic/antihistaminic agents other than Epinastine such as diphenhydramine hydrochloride, chlorpheniramine maleate, diphenylpyraline hydrochloride, and promethazine hydrochloride; cough suppressants such as dihydrocodeine phosphate, codeine phosphate, noscapine, pentoxyverine citrate, and dextromethorphan hydrobromide; expectorant drugs such as bromhexine hydrochloride, ambroxol hydrochloride, carbocysteine, and acetylcysteine; anticholinergic drug such as isopropamide iodide, and flutropium bromide; vitamins such as retinol, thiamine hydrochloride, riboflavin sodium phosphate, pyridoxine hydrochloride, cyanocobalamin, ascorbic acid,

EP 0 606 486 B1 discloses capsules being composed of hydroxypropylmethyl-cellulose, methylcellulose, hydroxypropylcellulose, starch, hydroxypropylstarch, and sodium alginate.

Principally all theses capsules can be take for the present invention, preferred are gelatine-capsules, in particular hard-gelatine capsules. Other preferred capsules are made of starch or of a cellulose-derivative like hydroxy-propylmethylcellulose.

Preferred standard capsules have the following physical characteristics:

Size	5	4	3	2	1	0
Filling-weight [mg]	65	100	150	185	250	340
Outside-Diameter [mm]						
Cap	4.89	5.31	5.82	6.35	6.90	7.63
Body	4.66	5.06	5.56	6.07	6.61	7.32
Length [mm] (± 0.3mm)						
Cap	6.05	7.47	8.23	9.17	10.01	11.18
Body	9.40	12.34	13.61	15.24	16.71	18.72
Body-Volume [ml]	0.13	0.21	0.28	0.37	0.49	0.68
Capsules-weight [mg] (±10%)	28.1	40.0	50.7	65.2	76.0	99.0

Among them capsule-size of 1 or 2 are preferred.

In case of a sustained release formulation it is preferred that the release of Pseudoephedrine and Methylephedrine takes place over 3 to 24, preferably 6 to 24, most preferably about 12 to 24 hours. The preferred dose regimen is a „once a day application", nevertheless how the formulation is applied.

In case of a bilayer tablet, each layer is in contact with each other in a portion of their surface, but provides independent release profiles for both active substances mentioned before.

Both layers A or B may further comprise pharmaceutically acceptable excipients and/or carriers.

The bilayer tablet according to the invention may additionally contain a tablet coating C consisting of pharmaceutically acceptable excipients, which mask the bitter taste of one of the active compounds.

In a preferred embodiment of the inventive bilayer tablet layer A comprises a decongestant effective amount of Pseudoephedrine or a pharmaceutically acceptable salt thereof and Methylephedrine or a pharmaceutical acceptable salt thereof in a matrix of a swellable hydrophilic polymer which provides a sustained release profile in a period of 3 to 24, preferably 6 to 18, most preferably about 12 hours.

In another application form the inventive composition may be formulated as a capsule. Such a capsule can provide the active ingredients either instantly or some of them are provided instantly and others are provided in a sustained manner. As outlined above it is preferred to formulate the active ingredients Pseudoephedrine (or its salts) and Methylephrine (or its salts) as a sustained releases form and Epinastine or its salts as immediate release form.

Preferably the capsules are made of materials that at least partially can be digested by humans. Such capsules f.e. are disclosed in EP 0143524. The latter discloses a two-part capsule of material which is easily digestible by humans.

EP 0460921 describes capsules of chitosan and starch, grain powder, oligosaccharides, methacrylic acid-methylacrylate, methacrylic acid-ethylacrylate, hydroxypropylmethylcelluloseacetate, -succinate or -phthaleate.

GB 938828 discloses capsules comprising water-soluble gelatine, methylcellulose, Polyvinylalkohol or water-soluble non-toxic thermoplasts.

dipotassium salt, trisodium 3-carboxy-5-hydroxy-1-p-sulphophenyl-4-p-sulfophenylazopyrazole, 6-hydroxy-5-((4-sulphonphenyl)azo-2-naphthalenesulphonic acid disodium salt and optionally aluminium lakes thereof. Magnesium stearate, talc and stearic acid are typical lubricants. Typical binders are povidone, and cornstarch.

Water and ethanol are examples of volatile components which can be used in the manufacture process of both layers to granulate powders. These volatile components are removed during processing and therefore do not appear in the finished product.

The tablet coating is optional since the presence of it does not modify significantly the release rates of the active substances present in the core layers. The presence of the coating is preferred because it masks the bitter taste of one of the active substances and enhances the properties of dosage form. Because of that a lot different coatings with different polymers, and plasticizers and other excipients could be used with the condition of not modifying significantly the release profile of the active substances present in the core tablet. A typical coating comprises a polymer such as hydroxypropylmethylcellulose and a plasticizer such as polyethylene glycol. Optional excipients could be added to the coating like antifoaming agents and opacifying agents. Example of an antifoaming agent is silicone. Examples of opacifying agents are Titanium dioxide, talc and aluminum lake dyes.

The inventive formulation also can be applied via a tablet comprising sustained release and non-sustained release granules or a capsule comprising the same.

In case of such a tablet, non-sustained release granules and sustained release granules, which are coated with a sustained release film are mixed with suitable excipients and then they are compressed as a tablet.

Similarly non-sustained release granules and sustained release granules which are coated with sustained release film are mixed and filled into a capsule.

A non-sustained release granule comprises an amount of Epinastine or a pharmaceutically acceptable salt thereof. Optionally it may comprises a portion of the

The sustained release layer A comprises beside the active ingredient(s) a swellable hydrophilic polymer.

Typical swellable hydrophilic polymers include cellulose ethers such as methylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, carboxymethylcellulose and carboxyethylcellulose or mixtures thereof. The use of hydroxypropylmethylcellulose (HPMC) is preferred. Particularly useful are the HPMC polymers HPMC USP2910 and USP2208 like for instance Methocel E5, E4M, E15M, K15M, and K100M supplied by the Dow Chemical Company. In the aforementioned abbreviations the designation "E" refers to USP2910 whereas "K" refers to USP2208. The number designation refers to the viscosity in a 2% aqueous solution (e.g. 5 designates a viscosity of 5 cps; 15M designates a viscosity of 15000 cps).

The excipients that could be optionally used in the sustained release layer A are insoluble polymers, soluble or insoluble fillers, antiadherents, coloring agents, lubricants and additional binders. Typical fillers are for example lactose, microcrystalline cellulose, dibasic calcium phosphate and cornstarch. Examples of antiadherents, which are used to prevent tablets from sticking to the tablet press, are colloidal silicon dioxide and talc. Magnesium stearate, talc and stearic acid are typical lubricants. Typical binders are povidone, and cornstarch.

The immediate release matrix layer B comprises beside the active ingredient different combinations of excipients. The excipients that could be optionally used in the immediate release layer B are insoluble polymers, soluble or insoluble fillers, antiadherents, lubricants, coloring agents, disintegrants and additional binders. Typical fillers are for example lactose, microcrystalline cellulose, dibasic calcium phosphate and cornstarch. Examples of antiadherents, which are used to prevent tablets from sticking to the tablet press, are colloidal silicon dioxide and talc. Typical disintegrants are crospovidone, sodium starch glycolate and crosscarmellose sodium. Typical coloring agents are selected from FD&C red 40 HT Aluminum lake, 2-hydroxy-1.1'-azonaphthalene-3.6.4'-trisulfonic acid trisodium salt, erythrosine, iron oxides, 1-(4-sulpho-1-naphthylazo)-2-naphthol-6.8-disulphonic acid trisodium salt, 2',4',5',7'-t trabromo-4.5.6.7-tetrachloro-fluorescein disodium salt, 2.4.5.7-Tetraiodo-3.6-dihydroxyxanthene-9-spiro-1'-(4',5',6',7'-tetrachloro-3'H-isobenzofuran-3'one

polyvinylpyrrolidone, polyethylene glycol. Typical plasticizers are glycerine fatty acid ester, triethyl citrate, propylene glycol, triacetin.

For any of the inventive application forms, bilayer tablet or other sustained release tablet, instant release-tablet or capsule any of the aforementioned ingredients can be taken, if appropriate.

In the context of the present invention capsules and tablets comprising sustained release and non-sustained release granules are preferred.

Examples

The invention will be further described by the following examples. These examples disclose certain preferred embodiments of the invention. The methods of manufacturing the compositions according to the invention like for instance granulation, tablet compression, tablet-coating etc. are well known to the person skilled in the art. Those skilled in the art will appreciate that various changes, modifications and substitutions can be made therein without departing from the spirit of the invention. Accordingly, it is intended that the invention be not limited to the following explicitly disclosed examples.

Example 1

Epinastine hydrochloride	15 g
Methylephedrine hydrochloride	150 g
Pseudoephedrine hydrochloride	275 g
Lactose	275 g
Microcrystalline cellulose	270 g
Magnesium stearate	15 g

The ingredients shown below are mixed evenly, 220 mg of the mixed powder obtained is filled in a capsule.

Example 2

Epinastine hydrochloride	18 g
Methylephedrine hydrochloride	160 g

total amount of Pseudoephedrine or a pharmaceutically acceptabl salt thereof and/or of the total amount of Methylephedrine or a pharmaceutically acceptable salt thereof, if necessary.

A sustained release granule comprises either a portion or the total amount of Pseudoephedrine or a pharmaceutically acceptable salt thereof and Methylephedrine or a pharmaceutically acceptable salt thereof.

Preferably the non-sustained release granules contain only Epinastine or a pharmaceutically acceptable salt thereof as active ingredient while the sustained release granules comprise the remaining active ingredients.

Any compounds conventionally used as a sustained-release coat can be used for the purpose of this invention. Specific examples which can be given include water insoluble polymers such as ethylcellulose, aminoalkyl methacrylate copolymer polyvinyl acetate, polyvinyl chloride, polyethylene, and the like; intestinally soluble polymers such as cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate, carboxymethylethylcellulose, styrene acrylic acid copolymer, methacrylic acid copolymer, maleic anhydrous acid copolymer, shellac, and the like; paraffin waxes such as paraffin, microcrystalline wax, and the like; higher alcohols, preferably saturated and unsaturated $C_8 - C_{26}$-alcohols, preferred unbranched and unsubstituted, such as stearyl alcohol, cetyl alcohol, and the like; esters of higher fatty acids, preferably saturated and unsaturated $C_8 - C_{26}$-acids, preferred unbranched and unsubstituted, such as glycerine fatty acid esters, hydrogenated oils, carnauba wax, beeswax, Japan (haze) wax, and the like; and higher fatty acids as defined above such as stearic acid, palmitic acid, myristic acid, behenic acid, and the like (or the sodium, calcium or magnesium salts of these higher fatty acids).

Furthermore, the excipients that could be optionally used in sustained release film are water soluble polymers, sugar alcohols, plasticizers, titanium oxide, talc, coloring agents and so on. Typical water soluble polymers and sugar alcohols are hydroxypropyl methylcellulose, hydroxypropylcellulose, methylcellulose,

Lactose	80 g
Mycrocrystalline cellulose	60 g
Magnesium stearate	6 g

The ingredients shown below are mixed, 300 mg of the mixed powder obtained are pressed as tablet by direct compression method.

Pseudoephedrine hydrochloride	275 g
Anhydrous caffeine	125 g
Lactose	360 g
Microcrystalline cellulose	300 g
Magnesium stearate	12 g

The ingredients shown below are mixed evenly, 250 mg of the mixed powder obtained is pressed as tablet by direct compression method.

Example 3

Ibuprofen	240 g
Isopropamide iodide	4 g
Epinastine hydrochloride	6 g
Methylephedrine hydrochloride	36 g
Pseudoephedrine hydrochloride	100 g
Noscapine hydrochloride	12 g
Anhydrous caffeine	40 g
Lactose	80 g
Mycrocrystalline cellulose	76 g
Magnesium stearate	6 g

The ingredients shown below are mixed, 300 mg of the mixed powder obtained are pressed as tablet by direct compression method.

Example 4

Acetoaminophen	160 g
Dihydrocodeine phosphate	8 g
Epinastine hydrochloride	4 g
Methylephedrine hydrochloride	20 g
Pseudoephedrine hydrochloride	60 g
Anhydrous caffeine	24 g
Vitamin B1 nitrate	8 g
Vitamin C	100 g
Corn starch	70 g

C. Coating

Film Coating	mg/ tablet
Methocel E5	7.50
Polyethylene Glycol 6000	0,985
Silicone antifoam S184	0.015
Total film coating	**8.50**

Total Film coated tablet	**408,50**

* PR means Premium grade and CR means Controlled Released grade.

Method of Manufacture

A. First layer:

A1. Dissolve povidone in a hydroalcoholic mixture;

A2. Blend Pseudoephedrine hydrochloride, Methylephedrine hydrochloride, a portion of the microcrystalline cellulose, lactose and Methocel K15M for 5-30 minutes in a suitable mixer.

A3. Use alcoholic or hydroalcoholic solution prepared previously in step A1 to granulate the powder mix of step A2.

A4. Dry and mill the granulation from step A3, using suitable size screen.

A5. Blend the screened granulation with a portion of the microcrystalline cellulose and colloidal silicon dioxide for 3-15 minutes.

A6. Add magnesium stearate and blend for 3-15 minutes.

B Second layer:

B1. Pass through a suitable screen Epinastine HCL, Allura red AC (FD & C red 40 HT) aluminum lake and microcrystalline cellulose. Blend for 5-30 minutes in a suitable mixer.

B2. Add lactose and povidone. Blend for 60 minutes 15-120 minutes in a suitable mixer.

B3. Add magnesium stearate. Blend for 3-20 minutes in a suitable mixer.

C. Compression:

Compress A and B into a suitable bilayer tableting machine in suitable size tablets.

Example 5 sustained release bilayer tablet

In any of the following examples the amounts of Epinastine, Pseudoephedrine and Methylephedrine can be adjusted to the amounts according to examples 1 to 4.

Core

A, First layer

Layer pseudoephedrine, Methylephedrine	**mg/tablet**
Pseudoephedrine hydrochloride	30.00
Methylephedrine hydrochloride	30.00
Methocel K 15 M PRCR *	99.00
Lactose Monohydrate	52.4
Microcrystalline cellulose	53.00
Colloidal silicon dioxide	0.825
Magnesium Stearate	1.375
Povidone	8.4
Total first layer	**275.00**

B. Second layer

Layer Epinastine	**mg / tablet**
Epinastine HCl	5.00
FD&C red 40 HT Aluminum lake (allura red AC)	0.19
Microcrystalline cellulose	35.00
Lactose Monohydrate	77.31
Povidone	6.25
Magnesium Stearate	1.25
Total second layer	**125.00**

Total core	**400.00**

Film Coating	mg/ tablet
Methocel E5	2.21
Polyethylene Glycol 6000	1.36
Talc	4.38
Titanium dioxide	0.55
Total film coating	**8.50**

Total Film coated tablet	**408.50**

* PR means Premium grade and CR means Controlled Released grade.

Method of Manufacture

A. First layer:

A1. Blend Pseudoephedrine hydrochloride, Methylephedrine hydrochloride, microcrystalline cellulose, lactose, colloidal silicon dioxide and HPMC K15M for 5-30 minutes in a suitable mixer.

A2. Add magnesium stearate and blend for 3-15 minutes.

B. Second layer:

B1. Pass through a suitable screen Epinastine HCl, and microcrystalline cellulose. Blend for 5-30 minutes in a suitable mixer.

B2. Add lactose. Blend for 60 minutes 15-120 minutes in a suitable mixer.

B3. Add magnesium stearate. Blend for 3-20 minutes in a suitable mixer.

C. Compression:

Compress A and B into a suitable bilayer tableting machine in suitable size tablets.

D. Coating

D1. Dissolve Methocel E5 and Polyethylene Glycol in suitable amount of water.

D2. Add Titanium Dioxide and Talc in suitable amount of water and mix

D3. Add 2. to 1. And mix.

D4. Coat tablets with the Methocel E5 /Polyethylene glycol solution from step D3. in a suitable coater.

D. Coating

D1. Dissolve Methocel E5 and Polyethylene Glycol in suitable amount of water.

D2. Dissolve silicone antifoam in suitable amount of isopropilic alcohol.

D3. Add 2. to 1. and mix.

D4. Coat tablets with the Methocel E5 /Polyethylene glycol solution from step D3. in a suitable coater.

Example 6 sustained release bilayer tablet

Core

A. First layer

	Mg/tablet
Pseudoephedrine hydrochloride	30.00
Methylephedrine hydrochloride	30.00
Methocel K 15 M PRCR *	99.00
Lactose Monohydrate	63.10
Microcrystalline cellulose	50.15
Colloidal silicon dioxide	1.375
Magnesium Stearate	1.375
Total first layer	**225.00**

B. Second layer

Layer Epinastine	**Mg / tablet**
Epinastine HCl	5.00
Lactose Monohydrate	84.20
Microcrystalline cellulose	35.00
Punceau 4R red aluminum lake	0.175
Magnesium Stearate	0.625
Total second layer	**125.00**

Total core	**400.00**

C. C ating

Example 8 sustained release bilayer tablet

Core

A. First layer

	Mg/tablet
Pseudoephedrine hydrochloride	30.00
Methylephedrine hydrochloride	30.00
Methocel K15 M PRCR	99.00
Lactose Monohydrate	49.60
Microcrystalline cellulose	49.90
Colloidal silicon dioxide	1.375
Povidone	13.75
Magnesium stearate	1.375
Total	**275.0 0**

* PR means Premium grade and CR means Controlled Released grade.

Second layer and coating are identical to example 5; the manufacture method was conducted analogously to the method outlined in example 5;

Example 9 sustained release bilayer tablet

Core

A. First layer

	Mg/tablet
Pseudoephedrine hydrochloride	30.00
Methylephedrine hydrochloride	30.00
Methocel K15M CR	165.00
Lactose	41.75
Talc	5.50
Magnesium Stearate	2.75
Total	**275.00**

* CR means Controlled Released grade.

Second layer and coating are identical to example 5; the manufacture method was conducted analogously to the method outlined in example 5;

Example 7 sustained release bilayer tablet

Core

A. First layer

	Mg/ tablet
Pseudoephedrine hydrochloride	30,00
Methylephedrine hydrochloride	30.00
Methocel K4M PRCR	123.75
Lactose Monohydrate	83.00
Talc	5,5
Magnesium Stearate	2,75
Total first layer	**275.00**

* PR means Premium grade and CR means Controlled Released grade.

Second layer and coating are identical to example 6; the manufacture method was conducted analogously to the method outlined in example 6;

Example 11 sustained release bilayer tablet

Core

A. First layer

	Mg/tablet
Pseudoephedrine hydrochloride	30.00
Methylephedrine hydrochloride	30.00
Methocel K15M CR	107.65
Dibasic Calcium phosphate	54.10
Ethylcellulose	20.00
Talc	5.50
Magnesium Stearate	2.75
Ethanol	s.q.
Total	**250.00**

* CR means Controlled Released grade.

Second layer and coating are identical to example 5; the manufacture method was conducted analogously to the method outlined in example 5;

Example 10 sustained release bilayer tablet

Core

A. First layer

	Mg/tablet
Pseudoephedrine hydrochloride	30.00
Methylephedrine hydrochloride	30.00
Methocel K15M CR	137.50
Microcrystalline Cellulose	69.25
Talc	5.50
Magnesium Stearate	2.75
Ethanol	sq.
Total	**275.00**

* CR means Controlled Released grade.

Second layer and coating are identical to example 5; the manufacture method was conducted analogously to the method outlined in example 5;

Second layer and coating are identical to example 5; the manufacture method was conducted analogously to the method outlined in example 5;

Example 14 sustained release bilayer tablet

Core

A. First layer

	Mg/tablet
Pseudoephedrine hydrochloride	30.00
Methylephedrine hydrochloride	30.00
Methocel K15M CR	103.25
Methocel K100M CR	34.40
Lactose	69.10
Talc	5.50
Magnesium Stearate	2.75
Ethanol	s.q.
Total	**275.00**

* CR means Controlled Released grade.

Second layer and coating are identical to example 5; the manufacture method was conducted analogously to the method outlined in example 5;

Example 12 sustained releas bilayer tablet

Core

A. First layer

	Mg/tablet
Pseudoephedrine hydrochloride	30.00
Methylephedrine hydrochloride	30.00
Methocel K15M CR	68.90
Methocel K100M CR	68.75
Lactose	69.10
Talc	5.50
Magnesium Stearate	2.75
Ethanol	s.q.
Total	**275.00**

* CR means Controlled Released grade.

Second layer and coating are identical to example 5; the manufacture method was conducted analogously to the method outlined in example 5;

Example 13 sustained release bilayer tablet

Core

A. First layer

	Mg/tablet
Pseudoephedrine hydrochloride	30.00
Methylephedrine hydrochloride	30.00
Methocel K100M CR	137.65
Lactose	69.25
Talc	5.50
Magnesium Stearate	2.75
Ethanol	s.q.
Total	**275.00**

* CR means Controlled Released grade.

Example 16 sustained release bilayer tablet

Core

A. First layer

	Mg/tablet
Pseudoephedrine hydrochloride	30.00
Methylephedrine hydrochloride	30.00
Methocel K15M CR	127.65
Lactose	19.85
Microcrystalline Cellulose	34.25
Talc	5.50
Magnesium Stearate	2.75
Ethanol	s.q.
Total	**250.00**

* CR means Controlled Released grade.

Second layer and coating are identical to example 5; the manufacture method was conducted analogously to the method outlined in example 5;

Example 17 sustained release bilayer tablet

Core

A. First layer

	Mg/tablet
Pseudoephedrine hydrochloride	30.00
Methylephedrine hydrochloride	30.00
Methocel K15M CR	127.65
Dibasic calcium phosphate	54.10
Talc	5.50
Magnesium Stearate	2.75
Ethanol	s.q.
Total	**250.00**

* CR means Controlled Released grade.

Example 15 sustained release bilayer tablet

Core

A. First layer

	Mg/tablet
Pseudoephedrine hydrochloride	30.00
Methylephedrine hydrochloride	30.00
Methocel K15M CR	117.65
Dibasic Calcium phosphate	54.10
Ethylcellulose	10.00
Talc	5.50
Magnesium Stearate	2.75
Ethanol	s.q.
Total	**250.00**

* CR means Controlled Released grade.

Second layer and coating are identical to example 5; the manufacture method was conducted analogously to the method outlined in example 5;

A2. Blend Epinastine hydrochloride and Pseudoephedrine hydrochloride, Methylephedrine hydrochloride in a suitable mixer and pulverise the powder mix.

A3. Produce spherical granules by spraying the solution prepared previously in step A1 over sucrose introducing the powder mix obtained from step A2.

A4. Dry and pass through granules from step A3 with suitable size screen to produce non-sustained release granules.

B. Sustained release granules

B1. Dissolve hydroxypropylcellulose in ethanol.

B2. Blend Pseudoephedrine hydrochloride, Methylephedrine hydrochloride in a suitable mixer.

B3. Produce spherical granules by spraying the solution prepared previously in step B1 over sucrose introducing the powder mix obtained from step B2.

B4. Dry and pass through granules from step B3 with suitable size screen

B5. Dissolve Methaacrylic acid copolymer, type B in ethanol and mix with glycerol esters of fatty acids and talc.

B6. Coat the granules obtained from step B4 with the solution prepared previously in step B5 to produce sustained release granules.

C. Capsulation

C1. Mix non-sustained release granules and sustained release granules with talc.

C2. Fill the mixture obtained from step C1 into capsules

Example 19

a) Non-sustained release granules: 2 capsules (size 1)

Epinastine hydrochloride	10.00 mg
Pseudoephedrine hydrochloride	18.00 mg
Methylephedrine hydrochloride	18.00 mg
Hydroxypropylcellulose	3.59 mg
Sucrose	499.41 mg
Total	**549.00 mg**

Second layer and coating are identical to example 5; the manufacture method was conducted analogously to the method outlined in example 5;

Example 18

a) Non-sustained release granules: 2 capsules (size 1)

Epinastine hydrochloride	10.00 mg
Pseudoephedrine hydrochloride	18.00 mg
Methylephedrine hydrochloride	18.00 mg
Hydroxypropylcellulose	3,59 mg
Sucrose	499.41 mg
Total	**549.00 mg**

b) Sustained release granules: 2 capsules (size 1)

Pseudoephedrine hydrochloride	42.00 mg
Methylephedrine hydrochloride	42.00 mg
Hydroxypropylcellulose	4.00 mg
Sucrose	67.00 mg
Methaacrylic acid copolymer,type B	40.60 mg
Glycerol esters of fatty acids	3.10 mg
Talc	1.30 mg
Total	**200 mg**

Capsulation

non-sustained relaes granules	549.00 mg
sustained relaes granules	200.00 mg
Talc	1.00 mg
Total	750.00 mg

Method of Manufacture

A. Non-sustained release granules

A1. Dissolve hydroxypropylcellulose in ethanol.

Methylephedrine hydrochloride	42.00 mg
Hydroxypropylcellulose	4.00 mg
Sucrose	67.00 mg
Methaacrylic acid copolymer,type B	30.45mg
Magnesium stearate	10.15 mg
Glycerol esters of fatty acids	3.10 mg
Talc	1.30 mg
Total	**200 mg**

Compression

non-sustained relaes granules	250.00 mg
sustained relaes granules	200.00 mg
Microcrystalline cellulose	126.00 mg
Croscarmellose sodium	12.00 mg
Talc	6.00 mg
Magnesium stearate	6.00 mg
Total	**600.00 mg**

Method of Manufacture

A. Non-sustained release granules

A1. Dissolve hydroxypropylcellulose in ethanol.

A2. Blend Epinastine hydrochloride and Pseudoephedrine hydrochloride, Methylephedrine hydrochloride, microcrystalline cellulose and lactose in a suitable mixer and knead the mixture with the solution from step A1.

A3. Dry and pass through granules obtained from step A2 with suitable size screen to produce non-sustained release granules

B. Sustained release granules

B1. Dissolve hydroxypropylcellulose in ethanol.

B2. Blend Pseudoephedrine hydrochloride ,Methylephedrine hydrochloride in a suitable mixer.

B3. Produce spherical granules by spraying the solution prepared previously in step B1 over sucrose introducing the powder mix obtained from step B2.

B4. Dry and pass through granules from step B3 with suitable size scre n

b) Sustained release granules: 2 capsules (size 1)

Pseudoephedrine hydrochloride	42.00 mg
Methylephedrine hydrochloride	42.00 mg
Hydroxypropylcellulose	4.00 mg
Sucrose	67.00 mg
Ethylcellulose	38.75 mg
Hydrooxypropylmethycellulose 2910	1.00 mg
Glycerol esters of fatty acids	2.25 mg
Talc	3.00 mg
Total	**200 mg**

Capsulation

non-sustained relaes granules	549.00 mg
sustained relaes granules	200.00 mg
Talc	1.00 mg
Total	750.00 mg

The manufacture method was conducted analogously to the method outlined in example 14.

Example 20

a) Non-sustained release granules

Epinastine hydrochloride	10.00 mg
Pseudoephedrine hydrochloride	18.00 mg
Methylephedrine hydrochloride	18.00 mg
Hydroxypropylcellulose	12.59 mg
Microcrystalline cellulose	178.91 mg
Lactose	12.5 mg
Total	**250.00 mg**

b) Sustained rel ase granules

Pseudoephedrine hydrochloride	42.00 mg

Claims

1) Oral pharmaceutical compositions comprising as pharmaceutically active compounds a combination of a) an antihistaminic-effective amount of Epinastine or a pharmaceutically acceptable salt thereof, b) a decongestant-effective amount of Pseudoephedrine or a pharmaceutically acceptable salt thereof and c) Methylephedrine or a pharmaceutically acceptable salt thereof and d) further comprising pharmaceutically acceptable carriers or excipients.

2) Oral pharmaceutical composition according to claim 1, characterised in that the daily dosage form is containing 2 to 25 mg of Epinastine or a pharmacologically permissive salts thereof.

3) Oral pharmaceutical composition according to claim 1 or 2, characterised in that the daily dosage form is containing 10 to 240 mg of Methylephedrine or a pharmacologically permissive salt thereof.

4) Oral pharmaceutical composition according to claim 1, 2 or 3, characterised in that the daily dosage form is containing 10 to 300 mg of Pseudoephedrine or a pharmacologically permissive salt thereof.

5) Oral pharmaceutical composition according to claims 1 to 4, characterised in that all active ingredients are formulated for instant release.

6) Oral pharmaceutical composition according to any of claims 1 to 4, characterised in that Epinastine or a pharmaceutically acceptable salt thereof is formulated for instant release and at least a portion of the other active ingredients Pseudoephedrine or a pharmaceutically acceptable salt thereof and Methylephedrine are formulated for sustained release.

7) Oral pharmaceutical composition according to claim 6, characterised in that the total amounts of Pseudoephedrine or a pharmaceutically acceptable salt thereof and Methylephedrine are formulated for sustained release.

B5. Dissolve Methaacrylic acid copolymer, type B in ethanol and mix with glycerol esters of fatty acids, magnesium stearate and talc.

B6. Coat the granules obtained from step B4 with the solution prepared previously in step B5 to produce sustained release granules.

C. Compression:

C1. Mix non-sustained release granules and sustained release granules with microcrystalline cellulose, croscarmellose sodium, talc and magnesium stearate.

C2. Compress the mixture into a suitable tableting machine in suitable size tablets.

polymers, paraffin waxes, higher alcohols, higher fatty acids and/or higher fatty acid esters.

16) Tablet comprising an oral formulation according to one of claims 1 to 8, characterised in that the ingredients are formulated as granules which are compressed to a tablet.

17) Tablet according claim 16, characterised in that the ingredients are formulated as sustained release and non-sustained release granules.

18) Tablet according to claim 16 or 17, characterised in that that the non-sustained granules are coated by a water insoluble polymers, intestinally soluble polymers, paraffin waxes, higher alcohols, higher fatty acids and/or higher fatty acid esters.

19) Use of a pharmaceutical composition according to one of claims 1 to 8, a bilayer tablet according to any of claims 9 to 11, a capsule according to any of claims 12 to 15 or a tablet according to any of claims 16 to 18 for the treatment of cold, for instance common cold, symptoms associated with cough, cold and flu, symptoms of allergic diseases such as saisonal allergic rhinitis, saisonal allergic conjunctivitis, allergic rhinitis, allergic congestion of the Eustachian tubes and / or other diseases from allergic origin deserving.

20) Use according claim 19 for the treatment of cough.

21) Use according claim 19 for the treatment of allergic diseases.

8) Oral pharmaceutical composition according to any of claims 1 to 7, characterised in that it represents a bilayer tablet.

9) Bilayer tablet according to claim 8, wherein a first layer A, providing for the sustained release of Pseudoephedrine and Methylephedrine or the corresponding pharmaceutical salts of the named active ingredients and wherein a second layer B, providing for the immediate release of epinastine, comprises an antihistaminic effective amount of Epinastine or a pharmaceutically acceptable salt thereof.

10) Bilayer tablet according to any of claims 8 or 9, characterised in that it additionally contains a tablet coating C consisting of pharmaceutically acceptable excipients.

11) Bilayer tablet according to any of claims 8 to 10, characterised in that layer A comprises Pseudoephedrine or a pharmaceutically acceptable salt thereof and Methylephedrine or a pharmaceutically acceptable salt thereof in a matrix of a swellable hydrophilic polymer.

12) Capsule comprising an oral formulation according to one of claims 1 to 8.

13) Capsule according to claim 12, characterised in that the material of the capsules comprises a compound being selected from the group of chitosan and starch, grain powder, oligosaccharides, methacrylic acid-methylacrylate, methacrylic acid-ethylacrylate, hydroxypropylmethylcelluloseacetate, -succinate or –phthaleate, polyvinylalcohol, water-soluble non-toxic thermoplasts, hydroxypropylmethyl-cellulose, methylcellulose, hydroxypropylcellulose, hydroxypropylstarch, sodium alginate, gelatine and hard-gelatine.

14) Capsule according to claim 12 or 13, characterised in that the ingredients are formulated as sustained release and non-sustained release granules.

15) Capsule according to claim 14, characterised in that the non-sustained granules are coated by a water insoluble polymers, intestinally soluble

Abstract

The present invention relates to novel oral pharmaceutical compositions comprising as pharmaceutically active compounds a combination of an antihistaminic-effective amount of Epinastine or a pharmaceutically acceptable salt thereof, a decongestant-effective amount of Pseudoephedrine or a pharmaceutically acceptable salt thereof and Methylephedrine (Methylephrine) in a decongestant-effective amount or a pharmaceutically acceptable salt thereof. The formulation further comprises suitable pharmaceutically acceptable carriers or excipients.